Genetic Epidemiology of Spontaneous Subarachnoid Hemorrhage

Nordic Twin Study

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Background and Purpose—It would be essential to clinicians, familial aneurysm study groups, and aneurysm families to understand the genetic basis of subarachnoid hemorrhage (SAH), but there are no large population-based heritability estimates assessing the relative contribution of genetic and environmental factors to SAH.

Methods—We constructed the largest twin cohort to date, the population-based Nordic Twin Cohort, which comprised 79 644 complete twin pairs of Danish, Finnish, and Swedish origin. The Nordic Twin Cohort was followed up for 6.01 million person-years using nationwide cause-of-death and hospitalization registries.

Results—One hundred eighty-eight fatal and 321 nonfatal SAH cases were recorded in the Nordic Twin Cohort. Thus, SAH incidence was 8.47 cases per 100 000 follow-up years. Data for pairwise analyses were available for a total of 504 SAH cases, of which 6 were concordant (5 monozygotic and 1 opposite sex) and 492 discordant twin pairs for SAH. The concordance for SAH in monozygotic twins was 3.1% compared with 0.27% in dizygotic twins, suggesting at most a modest role for genetic factors in the etiology of SAH. The population-based probability estimate for SAH in dizygotic siblings of a patient with SAH is 0.54%, and only 1 of 185 full siblings experience familial SAH. The corresponding risk of SAH in monozygotic twins is 5.9%. Model-fitting, which was based on the comparison of the few monozygotic and dizygotic pairs, suggested that the estimated heritability of SAH is 41%.

Conclusions—SAH appears to be mainly of nongenetic origin, and familial SAHs can mostly be attributed to environmental risk factors. **(*Stroke*. 2010;41:2458-2462.)**

Key Words: familial ■ intracranial aneurysm ■ SAH ■ twin ■ genetics

The incidence of subarachnoid hemorrhage (SAH) of approximately 7.8 cases per 100 000 person-years in non-Finnish countries[1] together with a 30-day mortality rate of 40% to 60% ranks SAH among the deadliest vascular emergencies. Compared with most Western countries, the risk of SAH is nearly 3 times as high (incidence 21.4 per 100 000 person-years) in Finland,[1] the reason for which remains unclear. Up to 90% of spontaneous SAH cases are due to rupture of an intracranial aneurysm.[2] Important modifiable risk factors for SAH include cigarette smoking (relative risk, 2.2 to 3.1), high blood pressure (relative risk, 2.5 to 2.6), and heavy (≥150 g/week) alcohol consumption (relative risk, 1.5 to 2.1).[3] It has been estimated that the population-attributable risk of cigarette smoking is 20% for SAH, whereas high blood pressure accounts for 17% and alcohol abuse for 11% to 21% of SAHs.[4]

Familial risk is defined as the probability of a healthy family member being affected by the same disease, which has already affected at least 1 other family member. Familial risk of SAH depends on a number of factors, including especially genetic and environmental factors as well as the number and ages of relatives at risk. In general, any population-based heritability estimate value of <50% indicates that environmental variance is greater than genetic variance. Given the

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Table 1. Characteristics of the Nordic Twin Cohort

	Danish Same-Sex Cohort	Danish Opposite-Sex Cohort	Finnish Cohort	Swedish Older Cohort	Swedish Younger Cohort
Year of birth	1870–1970	1870–1970	1880–1957	1886–1925	1925–1958
Baseline data collection	Varies	Varies	1975	1963	1972
Mean age in years at baseline (range)	Not applicable	Not applicable	36 (18–95)	49 (36–75)	28 (14–46)
End of the follow-up	12/31/2001	12/31/2001	12/13/2003 12/31/1995	12/13/2001	12/31/2001
No. twin individuals	52 386	27 530	26 326	21 163	32 495
No. complete pairs	26 184	13 765	12 898	10 581	16 236
Females, %	48	50	51	56	52
Monozygotic twins, %	35	0	31	35	39

*Hospitalized cases of SAH.

relatively low population-based incidence of SAH, it has been a challenge to estimate the genetic risk of SAH in relatives, the resolution of which could have significant implications on prophylactic screening protocols of intracranial aneurysms. Family history of SAH in first- and second-degree relatives has been reported to be a significant nonmodifiable risk factor with a 6.6-fold hazard ratio,[5] accounting for 11% of the population-attributable risk for SAH.[4]

Large twin cohorts provide a "shortcut" to carry out the estimation of heritability, defined as the proportion of the variance on an underlying liability to disease that is due to genomic effects and of environmentality, the proportion due to environment. Indeed, twin studies have been described as "the perfect natural experiment to separate familial resemblance from genetic influence,"[6] and large population-based twin studies can provide the best epidemiological evidence of familial clustering of any disease. Because of this, in an attempt to clarify the role of genetics in SAH, we performed the largest classical twin study to date consisting of Danish, Finnish, and Swedish population-based twin registers, which together comprised over 160 000 twin siblings.

Subjects and Methods

Study Subjects

Twin cohorts from Denmark, Finland, and Sweden have been described previously,[7–10] and these cohorts comprise the Nordic Twin Cohort. In brief, Finnish, Swedish, and Danish population-based cohorts have existed for many decades and they include virtually all the same-sex twins in the relevant birth cohorts, whereas the Danish cohort comprises not only same-sex, but also opposite-sex twins. The follow-up mortality data were obtained by linkage to computerized nationwide cause-of-death databases using the unique personal identifiers assigned to each citizen in each country. Nonfatal SAH cases were derived from national hospital discharge registers, which cover virtually the whole populations of the countries in the study. The data were available up to the end of 2001 in Denmark and Sweden and up to the end of 2003 in Finland for fatal SAH. For nonfatal Finnish SAH cases, the data were updated at the end of 1995. The pooled data comprised 79 664 complete twin pairs and 160 438 individuals including a small number of twins with missing information on their cotwin. Of all subjects, 51% were women. Incident cases of SAH as well as all deaths with the underlying cause of death coded as an SAH or hospitalization for an SAH (the main cause) were classified as cases. After an SAH (fatal or nonfatal) in a twin, the median follow-up time for the cotwin was computed as the time until an SAH (fatal or nonfatal) occurred, emigration, or end of follow-up. Characteristics of the twin cohorts are presented in Table 1.

Determination of Zygosity

For all 3 national cohorts, zygosity was determined by standardized questionnaire methods. The questionnaire methods have been validated,[11–13] and they correctly classify >95% of twin pairs as monozygotic (MZ) or dizygotic (DZ).

Data Analysis

Nonfatal and fatal SAHs were recorded during the follow-up time, which was different for every cohort (Table 1). Twin pairs were defined as discordant twin pairs for SAH if only 1 twin had an SAH during the follow-up time regardless of whether the cotwin had died from another cause. Twin pairs were concordant for SAH if both twins had an SAH. Sex, zygosity, and age effects on the incidence of SAH were tested by a Cox proportional hazard model, for which the follow-up time was calculated from the time point of the baseline measurement to the date of SAH, death from other causes, emigration, or the end of the follow-up period. The effect of the twin pair sample design was taken into account using the cluster option of the Stata statistical package (Version 9.2). The analyses were adjusted for birth date. Study cohort and sex in the pooled analyses for men and women were included as a stratum variable, that is, allowing its own baseline hazard for each group. Proportional hazard assumptions of SAH incidence were not violated for zygosity ($P=0.60$) or sex ($P=0.40$) when tested using Schoenfeld residuals.

Risk and Genetics of SAH

Two different estimators of the familial risk of SAH were used. To estimate the risk that a twin is affected given an affected cotwin, probandwise concordance was computed by dividing the number of cases among concordant twin pairs by the total number of cases.[14] All cases were ascertained independently, and estimates were computed separately for MZ and DZ pairs. The tetrachoric correlation of the pairwise (twin 1 versus twin 2 and affected versus unaffected, 2-by-2 table) distribution of cases in MZ and DZ pairs was computed as an estimate of the underlying, latent liability to SAH based on a threshold model of the disease.[15] Based on these contingency tables from MZ and DZ tables, standard model-fitting methods for additive genetic and environmental components of variance were fit using the Mx, a program for analysis of twin and family data.[16,17] All other analyses were done using the Stata statistical package (Version 9.2).

Results

The total number of twin subjects with SAH in the Nordic Twin Cohort was 509, but the follow-up data of cotwins were not available for 5 patients, and they were thus excluded from all pairwise analyses. The follow-up time was 6.01 million person-years for all individuals (Table 2). Of 509 twins with an SAH, 295 (58%) were female and 214 (42%) were male. SAH incidence in the Nordic Twin Cohort was 8.47 cases per 100 000 follow-up years (26.74, 12.43, 15.56, and 4.27 cases

Table 2. Follow-Up Times of the Cohorts, Concordant Twin Pairs for SAH, the Median Age at Diagnosis of Nonfatal SAH, and the Median Age of Death From SAH Among the 79 664 Twin Pairs

	Danish Same-Sex Cohort	Danish Opposite-Sex Cohort	Finnish Cohort	Swedish Older Cohort	Swedish Younger Cohort
Follow-up time, million person-years	2.58	1.24	0.65 0.51*	0.60	0.94
No. fatal SAH cases	29	19	60	49	31
No. concordant fatal pairs	0	1	0	0	1
No. all SAH cases	96	67	137	93	116
No. concordant pairs	2	1	0	2	1
Age of death from SAH in years and IQR†	57.9 (47.5–72.1)	46.0 (41.3–51.6)	56.1 (46.7–68.2)	69.5 (62.8–78.1)	50.0 (39.7–54.3)
Age at diagnosis of all SAHs in years and IQR†	54.5 (41.8–66.8)	46.0 (38.3–52.3)	51.9 (41.0–64.9)	69.8 (63.5–77.4)	50.0 (41.0–56.9)
Cotwin follow-up time in years and IQR†	7.9 (4.3–13.5)	8.9 (3.8–16.3)	8.6 (5.6–19.0)	12.6 (6.7–18.0)	10.2 (3.8–19.8)

*Hospitalized cases of SAH.
†Median together with interquartile range (IQR) (ie, lower [25th percentile] and upper [75th percentile] quartiles).

per 100 000 follow-up years in the Finnish, Swedish younger, Swedish older, and Danish cohorts, respectively; if the follow-up for the Danish cohort is started after the age of 20 years, the incidence is 7.16 cases per 100 000 follow-up years; see the Figure). The hazard ratio for women compared with men was 1.36 (95% CI, 1.10 to 1.69) for SAH incidence, whereas no difference in age- and sex-adjusted SAH incidence and mortality was found between MZ and DZ twin individuals in the pooled data ($P=0.09$ and $P=0.24$, respectively). The median age at SAH diagnosis was 53.6 years (interquartile range, 43.0 to 65.5 years; Table 2).

We identified only 6 twin pairs (12 twin subjects) concordant for SAH, and 5 of these were MZ twin pairs (Table 2). Patient characteristics for the concordant twin pairs are depicted in Table 3. In the 6 concordant pairs, the median time between the onset of SAH in both twin siblings was 3.5 years (range, 0 to 13 years). In comparison, the median follow-up time for all cotwins after SAH in the other twin (index case) was nearly 3-fold (9.7 years; interquartile range, 3.5 to 16.3 years; Table 2), which implies that a longer follow-up would unlikely show more concordant pairs. The probandwise concordance for all cases was 5.9% in MZ pairs.

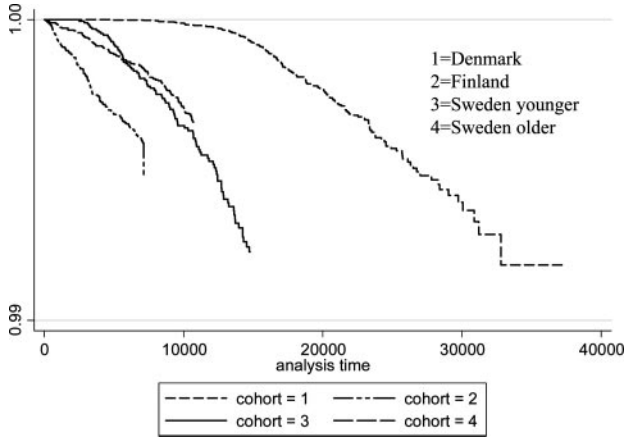

Figure. Kaplan–Meier survival estimates of the study cohorts.

Furthermore, the tetrachoric correlation in liability was 0.42 (95% CI, 0.24 to 0.56). For DZ pairs, the probandwise concordance was 0.54%, and the tetrachoric correlation in liability was 0.054 (95% CI, 0.0 to 0.26). Of the 492 discordant twin pairs (147 MZ and 345 DZ pairs), 184 (55 MZ and 129 DZ pairs) were discordant for fatal SAH (Table 2). Based on the comparison of the few MZ and DZ pairs, model-fitting estimate of heritability was 41% (95% CI, 23.7% to 55.5%).

Discussion

In this first and only large population-based heritability study assessing the relative contribution of genetic factors to SAH, we identified only 6 (1.2%) concordant pairs (5 MZ and opposite sex) of 498 twin pairs with SAH. Only 1 concordant MZ pair was relatively young at the time of SAH. The probandwise concordance value of 0.54% for DZ twins depicts the probability (recurrence risk) of SAH in full (same father and mother) singleton siblings, who, like DZ twins, share 50% of their segregating genes. This means that in families with 1 SAH patient, only 1 of 185 siblings experiences SAH. For MZ twins, who share, in addition to the genetic sequence, numerous environmental exposures and experiences, the probandwise concordance value was 5.9%, which means that every 17th MZ twin will experience an SAH after an occurrence of an SAH in the cotwin. The MZ tetrachoric correlation value (42%) implies a moderate size

Table 3. Patient Characteristics of Concordant Twin Pairs

Nationality	Zygosity	Sex	Age at Death	Age at SAH Diagnosis
Denmark	DZ	M/F	53/52	53/52
Denmark	MZ	M/M	49/48	48/48
Denmark	MZ	M/M	…/…	72/68
Finland	MZ	F/F	65/77	64/72
Finland	MZ	F/F	85/87	85/82
Swedish young	MZ	F/F	34/21	34/21

M indicates male; F, female.

broad-sense heritability (additive and nonadditive factors), which can result from additive genetic effects, genetic effects due to dominance, and genome–environment interaction effects shared by the twins. If the heritability was due only to additive genetic effects, the tetrachoric correlation in the DZ pairs should be 0.21. However, it was considerably lower (0.054), which implies the presence of effects due to dominance or the combination of genes at multiple loci. Model-fitting based on the comparison of the few MZ and DZ pairs showed that the estimated heritability was 41% (95% CI, 23.7% to 55.5%), which is very similar to the MZ tetrachoric correlation value. Previously, we have reported that the estimated heritability for prostate cancer, colorectal cancer, and breast cancer is 42%, 35%, and 27%, respectively.[10]

The strengths of our study include: (1) the population-based study cohorts with both fatal and nonfatal SAH cases; (2) the exceptionally large number of twins surveyed; (3) the satisfactory number of SAH events found among twins; (4) the reliable estimate of the incidence rate of SAH (8.47 cases per 100 000 follow-up years) in comparison with previous reports; 5) the long-term (almost lifetime) prospective follow-up of unaffected cotwins; 6) the similar centralized and high-quality cause-of-death and hospitalization registers, which have been widely used in thousands of previous studies in Nordic countries; and 7) the presence of the middle-aged large birth cohort. Because being a sibling of an affected relative has been reported to increase the risk of having an aneurysm or SAH more than being a parent or child,[18–20] the strength of evidence from our study of twin siblings is even more significant. The fact that twins are siblings of the same age eliminates the possibility of large phenotypic differences related to age differences, which complicate the analyses of genetic studies in singleton siblings and nuclear families. In addition, the systematic ignoring of extramarital paternity in family-based studies of heritability may result in some bias, whereas twin siblings rarely have different fathers.

The major drawbacks include the following: (1) discordant cotwins were not traced (practically impossible) to check whether preventive treatments for SAH had been given; (2) the relatively small proportional representation of young (<25 years of age) individuals in the cohorts; (3) surviving discordant cotwins were not invited to have an MRI angiogram to estimate the familial prevalence of aneurysms (which was not the purpose of this study); and (4) register-based diagnoses may contain errors. It is very unlikely that a significant number of endo- or exovascular procedures had been conducted before the rupture of an aneurysm to prevent a SAH in a discordant cotwin because 62% of the SAH incidents happened before 1993 when screening of family members was not a routine procedure nor a recommendation in Nordic countries. We believe that it is highly unlikely that the possible ignoring of rare events of SAHs at young ages may have affected our conclusions drawn.

Due to inevitable difficulties in conducting epidemiological studies on a rare, dichotomous and complex disease trait, some methodological shortcomings may have influenced previous interpretations. It has been virtually impossible to conduct a large enough population-based familial SAH study containing multiple affected individuals and longitudinal (several decades of follow-up) family data. Such a study cannot be done either at present or in the future, because many unruptured familial and incidental intracranial aneurysms are currently treated. Previous reports suggest that familial (at least 1 first-degree relative with SAH) occurrence of SAH is an important nonmodifiable risk factor for SAH.[5,20–22] Understandably, none of these studies have been able to control (1) risk factors (ie, confounding factors including cigarette smoking, high blood pressure, heavy alcohol consumption) among study and control subjects; (2) the number of full-sisters and other first-degree family members of the cases and control subjects when reporting incidence of SAH in families; and (3) consanguinity among family members. In accordance with our results, a recent large population-based (hospital-admitted, mainly nonfatal index cases) case–control (matched for age and sex, not for risk factors) study of the risk of familial SAH reported that only 10 (0.19%) of 5282 hospital-admitted patients with SAH have ≥2 first-degree relatives with an SAH (ie, ≥3 patients with SAH in the family), and 156 (2.95%) patients with SAH have 1 affected first-degree relative in the family.[23] In total, only 166 (3.14%) of 5282 patients with SAH have ≥1 affected first-degree family members.[23] The OR (not relative risk) of familial SAH for individuals with ≥1 affected first-degree relatives was 2.28 when compared with age- and sex-matched control subjects (ie, no adjustment for, for example, confounding risk factors), of which 1.41% had SAH cases in the family.[23] If the lifetime relative risk of SAH of a family member was 2-fold or even 15-fold higher than in the general population, for which the lifetime risk has been estimated to be 0.7%,[23] the absolute lifetime risk of SAH would be 1.4% and 10.5%, respectively. The recent population-based data suggest an absolute lifetime risk of SAH of 26% (OR, 51.0) for individuals with ≥2 first-degree relatives with SAH.[23] This very high lifetime risk estimate surely warrants screening programs for these rare SAH families.

Our results with the heritability estimate of 41% suggest that there is a moderate role for genetic factors in the etiology of SAH, whereas environmental factors play a significant role in SAH susceptibility at the population level. This relatively low heritability estimate for a complex trait suggests that very large genomewide association studies, similar to recent studies of intracranial aneurysms,[24,25] or whole genome linkage studies are necessary to identify genomic variants and candidate genes underlying the risk for SAH. Alternatively, genetic studies should focus on identifying rare variants in the families with multiple affected members.

Summary

In brief, our results together with the previous results[23] suggest that a positive family history accounts for, at the most, only a small percentage of SAHs, not for 11% of the population-attributable risk for SAH.[4] Of these rare familial SAH cases, possibly only a minority is due to the clustering of susceptibility genes. It is conceivable that familial clustering of confounding risk factors (eg, cigarette smoking, high blood pressure, and heavy alcohol consumption) makes a significant contribution to previously reported incidence rates

of familial SAHs. On the basis of current evidence, screening of familial aneurysms may be warranted at least for first-degree family members with ≥2 SAHs in the family and to a monozygotic sibling of a MZ twin with a positive history of SAH.

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Disclosures

None.

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Abstract

自然発症くも膜下出血の遺伝疫学 ― 北欧双生児研究

Genetic Epidemiology of Spontaneous Subarachnoid Hemorrhageke ― Nordic Twin Study

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背景および目的：医師や家族性動脈瘤研究グループ，動脈瘤の家系に属する人々にとって，くも膜下出血（SAH）の遺伝的基盤を理解することは不可欠であると考えられる。しかし，一般住民を対象にSAHに対する遺伝的要因と環境要因の相対的寄与率を検討し，遺伝率を推定した大規模研究は行われていない。

方法：北欧双生児コホートは，一般住民を対象とした過去最大規模の双生児コホートであり，デンマーク，フィンランド，スウェーデンで生まれたすべての双生児79,644組で構成されている。この北欧双生児コホートを対象に，全国死因登録簿および入院登録簿を用いて，合計601万人・年の追跡調査を行った。

結果：北欧双生児コホートから致死的SAH 188例および非致死的SAH 321例の記録が得られた。100,000追跡調査年あたりのSAH発症率は8.47件であった。合計504組のSAH症例についてペア解析のデータが得られ，このうち6組はともにSAHを発症し（5組は一卵性，1組は異性の二卵性），492組は一方のみがSAHを発症していた。SAHの一致率は，一卵性双生児が3.1％，二卵性双生児が0.27％で，SAH発症における遺伝的要因の役割はさほど大きくないと思われた。二卵性双生児の場合，一般人口の値に基づき推定した患者の同胞のSAH発症確率は0.54％であり，同胞185例のうち1例が家族性SAHを発症する程度である。これに対し，一卵性双生児の場合の上記リスク値は5.9％であった。このように少数の一卵性双生児と二卵性双生児の比較に基づきモデルを構築した結果，SAHの遺伝率は41％と推測された。

結論：SAHは主に遺伝以外の原因によって生じるようであり，家族性SAHは主として環境危険因子に起因していると考えられる。

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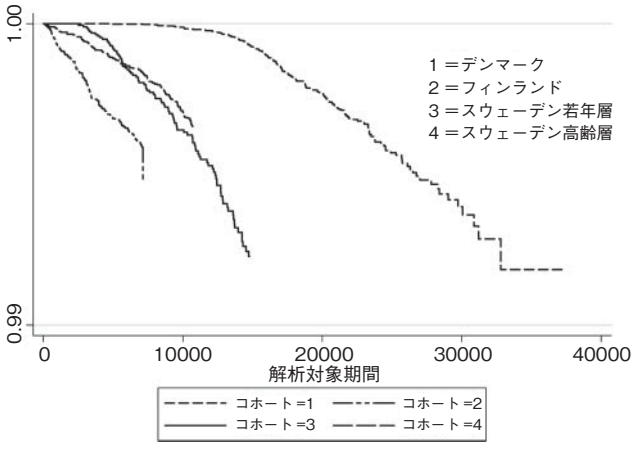

図　本研究コホートのKaplan-Meier生存推定値。

表3　ともにSAHを発症した双生児の患者特性

国籍	一卵性／二卵性	性別	死亡年齢	SAH診断年齢
デンマーク	DZ	M/F	53/52	53/52
デンマーク	MZ	M/M	49/48	48/48
デンマーク	MZ	M/M	…/…	72/68
フィンランド	MZ	F/F	65/77	64/72
フィンランド	MZ	F/F	85/87	85/82
スウェーデン若年層	MZ	F/F	34/21	34/21

MZ：一卵性，DZ：二卵性，M：男性，F：女性。